Debulking Of Chronic Total Occlusion with Rotational or Directional Atherectomy before Stenting Trial (DOCTORS Trial)
Background

PCI of CTO is associated with

- an acceptable success rate
- a favorable long-term patency by primary stenting
- a high revascularization rate due to restenosis
Hypothesis

Plaque debulking of CTO facilitates subsequent dilatation by balloon angioplasty and stenting and provides a better long-term angiographic outcome compared with primary stenting.
This study aimed to examine the impact of pre-stent plaque debulking of CTO by rotational or directional atherectomy (RA or DCA) on restenosis reduction in a multi-center randomized study.
### Study Design

- **Prospective**
- **Multi-center**
- **Randomized**
- **Any stent(s)**

<table>
<thead>
<tr>
<th>Debulking arm</th>
<th>vs</th>
<th>Non-debulking arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA or DCA</td>
<td></td>
<td>Stenting alone</td>
</tr>
<tr>
<td>before stenting</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*(Decision making by operator)*
Inclusion Criteria

- Definition of CTO

  1. TIMI flow grade = 0 or 1
  2. Estimated occluded duration > 1 month
     or unknown

- Occlusion length < 20 mm

- Suitable morphology for rotational or directional atherectomy

- Suitable morphology for stenting
Exclusion Criteria

- Reference diameter < 2.0 mm
- ACS culprit lesion
- Wire passed through the false lumen
- Bypass graft
- Occluded vessel supplied from intact bypass graft
- Instent occlusion
- Unsuitable morphology for atherectomy devices
- Unsuitable morphology for stenting
Procedural Sequence

- Successful crossing of CTO with conventional guide wire
- Judgement of RA or DCA application (by IVUS guidance)

Enrollment

Randomization

Debulking arm
- RA or DCA
- POBA, if necessary
- Stenting
- Adjunctive POBA, if necessary

Non-debulking arm
- POBA
- Stenting
- Adjunctive POBA, if necessary

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DOCTORS Investigators
Endpoints

Primary endpoint

- Angiographic restenosis at 6 months

Secondary endpoint

- MACE, TLR, TVR by 1 year
Study Organization

Principle Investigators

Etsuo Tsuchikane, MD  Toyohashi Heart Center
Yung-Sheng Hsu, MD  Shiga Medical Center for Adults
Kinzo Ueda, MD  Takeda Hospital

Safety Committee

Tetsu Yamaguchi, MD  Toranomon Hospital

QCA Core Laboratory

Takaaki Isshiki, MD  CARDIOCORE JAPAN (CMS-MEDIS)

Clinical Data Analysis

MEDICAL TOKEI Co. Ltd
Study Institutions

Japanese 21 Centers
Study Investigators

- Osaka Medical Center for Cancer and CVD
- Toyohashi Heart Center
- School of Medicine, Keio University
- Kyoto Katsura Hospital
- Niigata City General Hospital
- Takeda Hospital
- Showa General Hospital
- Nagoya Kyoritsu Hospital
- Sakurabashi Watanabe Hospital
- Shiga Medical Center for Adults
- Yamada Red Cross Hospital
- School of Medicine, Showa University
- National Nagasaki Medical Center
- Himeji Cardiovascular Center
- Toyooka Hospital
- Hoshi Sogo Hospital
- The Cardiovascular Institute
- Rinku General Medical Center
- Teine Keijinkai Hospital
- National Toyohashi Higashi Hospital
- Iwate Prefectural Central Hospital

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Kinzo Ueda, MD
Takahiro Tanaka, MD
Tetsuo Matsubara, MD
Kenshi Fujii, MD
Yung-Sheng Hsu, MD; Hideo Tamai, MD
Hideo Nishikawa, MD
Yuji Hamazaki, MD
Koji Oku, MD
Takatoshi Hayashi, MD
Yoshinori Yasaka, MD
Mikihiro Kijima, MD
Tadanori Aizawa, MD
Satoru Sumitsuji, MD
Mitsugu Hirokami, MD
Hiroaki Hosokawa, MD
Eiji Nozaki, MD; Kenji Tamaki, MD

- **RA indicated**: 177
  - Randomization: 90
  - Debulking arm: 138
- **DCA indicated**: 89
  - Randomization: 48
  - Non-debulking arm: 128

- Protocol violation: 10

Total enrolled: 276
### Patients Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Debulking</th>
<th>Non-debulking</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>138</td>
<td>128</td>
<td></td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>84.1%</td>
<td>81.3%</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Age (y.o.)</strong></td>
<td>64±9</td>
<td>65±9</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Prior MI</strong></td>
<td>57.2%</td>
<td>57.0%</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Prior CABG</strong></td>
<td>7.2%</td>
<td>7.0%</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Prior PCI</strong></td>
<td>36.2%</td>
<td>28.9%</td>
<td>NS</td>
</tr>
<tr>
<td><strong>UA</strong></td>
<td>7.2%</td>
<td>7.8%</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Multivessel</strong></td>
<td>68.1%</td>
<td>68.0%</td>
<td>NS</td>
</tr>
<tr>
<td><strong>HT</strong></td>
<td>58.0%</td>
<td>52.3%</td>
<td>NS</td>
</tr>
<tr>
<td><strong>DM</strong></td>
<td>34.8%</td>
<td>38.3%</td>
<td>NS</td>
</tr>
<tr>
<td><strong>HL</strong></td>
<td>57.2%</td>
<td>46.9%</td>
<td>NS</td>
</tr>
<tr>
<td><strong>H/O smoking</strong></td>
<td>51.4%</td>
<td>44.5%</td>
<td>NS</td>
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</table>
# Lesion Characteristics

<table>
<thead>
<tr>
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<th>Debulking</th>
<th>Non-debulking</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>138</td>
<td>128</td>
<td></td>
</tr>
<tr>
<td>Target vessel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCA / LAD / LCx</td>
<td>33 / 53 / 14%</td>
<td>39 / 48 / 13%</td>
<td>NS</td>
</tr>
<tr>
<td>De novo</td>
<td>89.1%</td>
<td>89.8%</td>
<td>NS</td>
</tr>
<tr>
<td>OMI related</td>
<td>55.1%</td>
<td>56.3%</td>
<td>NS</td>
</tr>
<tr>
<td>Calcified</td>
<td>61.6%</td>
<td>62.5%</td>
<td>NS</td>
</tr>
<tr>
<td>Jeopardized collateral</td>
<td>41.3%</td>
<td>38.3%</td>
<td>NS</td>
</tr>
<tr>
<td>Proximal tortuosity</td>
<td>37.0%</td>
<td>27.3%</td>
<td>NS</td>
</tr>
<tr>
<td>Bending (&gt;45 degree)</td>
<td>6.5%</td>
<td>3.1%</td>
<td>NS</td>
</tr>
</tbody>
</table>
## Lesion Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Debulking</th>
<th>Non-debulking</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td><strong>Number</strong></td>
<td>138</td>
<td>128</td>
<td></td>
</tr>
<tr>
<td><strong>TIMI=1</strong></td>
<td>18.1%</td>
<td>14.8%</td>
<td>NS</td>
</tr>
<tr>
<td><strong>TIMI=0</strong></td>
<td>81.9%</td>
<td>85.2%</td>
<td></td>
</tr>
<tr>
<td><strong>Occlusion length</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 10mm</td>
<td>40.6%</td>
<td>40.6%</td>
<td>NS</td>
</tr>
<tr>
<td>10 ≤ , &lt; 20mm</td>
<td>59.4%</td>
<td>59.4%</td>
<td></td>
</tr>
<tr>
<td><strong>Lesion length</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 20mm</td>
<td>39.9%</td>
<td>35.9%</td>
<td>NS</td>
</tr>
<tr>
<td>≥ 20mm</td>
<td>60.1%</td>
<td>64.1%</td>
<td></td>
</tr>
<tr>
<td><strong>Occlusive duration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 3M</td>
<td>5.1%</td>
<td>5.5%</td>
<td>NS</td>
</tr>
<tr>
<td>≥ 3M</td>
<td>16.6%</td>
<td>16.4%</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>78.3%</td>
<td>78.1%</td>
<td></td>
</tr>
</tbody>
</table>
Conventional Wires Used

Debulking arm

Non-debulking arm

- **Soft**
- **Intermediate**
- **Standard**
- **Super hard**

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RA Procedural Results

1. Pre-dilatation: 69.2%
2. Wire exchange success: 100%
3. Max. burr size: 1.84±0.21mm
4. Multiple burrs: 51.6%
   Number of used burrs: 1.51±0.50

5. Total ablation time: 102.5±85.3 sec.

6. Max. drop in RPM: 6800±4000 rpm

7. Complications during RA
   1) pacing 7.7% (6)
   2) spasm 6.6% (6)
   3) side branch occlusion 1.1% (1)
   4) no flow 0%
   5) perforation 0%
1. Pre-dilatation: 82%
2. Pre-dilatation balloon: $1.73 \pm 0.41$ mm
3. Wire used

- Grandslam
- Flexi-wire
- Platinum plus
- Iron man
- Others
4. Atherocatheter used

5. Max. cutting pressure: 54.9±31.1 psi

6. Complications during DCA

1) spasm \hspace{1cm} 2\% \ (1)

3) side branch occlusion \hspace{1cm} 2\% \ (1)

4) no flow \hspace{1cm} 4\% \ (2)

5) perforation \hspace{1cm} 0\%
## Stenting Procedural Results

<table>
<thead>
<tr>
<th></th>
<th>Debulking</th>
<th>Non-debulking</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>138</td>
<td>128</td>
<td></td>
</tr>
<tr>
<td><strong>Delivery success</strong></td>
<td>100%</td>
<td>99.2%</td>
<td></td>
</tr>
<tr>
<td><strong>Multiple stents</strong></td>
<td>21.7%</td>
<td>27.5%</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>Number of stents</strong></td>
<td>1.23±0.46</td>
<td>1.31±0.54</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>Stent size (mm)</strong></td>
<td>3.46±0.47</td>
<td>3.39±0.42</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>Total length of stents (mm)</strong></td>
<td>25.7±11.0</td>
<td>28.2±11.7</td>
<td><strong>0.076</strong></td>
</tr>
<tr>
<td><strong>Stenting pressure (atm)</strong></td>
<td>11.7±3.4</td>
<td>11.9±3.9</td>
<td>0.65</td>
</tr>
<tr>
<td><strong>Post dilatation</strong></td>
<td>63.8%</td>
<td>65.4%</td>
<td>0.79</td>
</tr>
<tr>
<td><strong>Post dilatation balloon (mm)</strong></td>
<td>3.45±0.45</td>
<td>3.42±0.44</td>
<td>0.62</td>
</tr>
<tr>
<td><strong>Post dilatation pressure (atm)</strong></td>
<td>12.9±4.3</td>
<td>13.6±4.5</td>
<td>0.32</td>
</tr>
</tbody>
</table>
### Final Procedural Results

<table>
<thead>
<tr>
<th></th>
<th>Debulking</th>
<th>Non-debulking</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>138</td>
<td>128</td>
<td></td>
</tr>
<tr>
<td><strong>Lesion unsuccessful</strong></td>
<td>1.4% (2)</td>
<td>1.6% (2)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Flow disturbance</strong></td>
<td>1.4% (2)</td>
<td>0.8% (1)</td>
<td>0.49</td>
</tr>
<tr>
<td><strong>Residual stenosis</strong></td>
<td>0</td>
<td>1.6% (2)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>MACE</strong></td>
<td>0.7% (1)</td>
<td>0</td>
<td>NS</td>
</tr>
</tbody>
</table>
## In-Hospital Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Debulking</th>
<th>Non-debulking</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>138</td>
<td>128</td>
<td></td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>0.7% (1*)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td><strong>CABG</strong></td>
<td>0.7% (1)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Q-wave MI</strong></td>
<td>1.4% (2*)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Subsequent PCI</strong></td>
<td>0</td>
<td>0.8% (1)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*same patient

---

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### Clinical 6Mo Fu Results after Discharge

<table>
<thead>
<tr>
<th>Event</th>
<th>Debulking</th>
<th>Non-debulking</th>
<th>P value</th>
<th>N.S.</th>
</tr>
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<tbody>
<tr>
<td>Number</td>
<td>132</td>
<td>114</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q-wave MI</td>
<td>0.8% (1)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>0</td>
<td>1.8% (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any event</td>
<td>0.8% (1)</td>
<td>1.8% (2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
TLR and TVR in Fu CAG Pts

ALL

TLR

Debulking
Non-debulking

TVR

Debulking
Non-debulking

18.8%
29.1%
21.9%
36.4%

P=0.061
P=0.014

(n=128) (n=110)
(n=128) (n=110)
TLR and TVR in Fu CAG Pts

RA indicated

<table>
<thead>
<tr>
<th></th>
<th>Debulking</th>
<th>Non-debulking</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TLR</strong></td>
<td>20.7%</td>
<td>29.7%</td>
</tr>
<tr>
<td>(n=82)</td>
<td>(n=74)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TVR</strong></td>
<td>23.2%</td>
<td>36.5%</td>
</tr>
<tr>
<td>(n=82)</td>
<td>(n=74)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P = 0.20

P = 0.069
TLR and TVR in Fu CAG Pts

**DCA indicated**

<table>
<thead>
<tr>
<th></th>
<th>Debulking</th>
<th>Non-debulking</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLR (n=46)</td>
<td>15.2%</td>
<td>19.6%</td>
</tr>
<tr>
<td>TVR (n=36)</td>
<td>27.8%</td>
<td>36.1%</td>
</tr>
</tbody>
</table>

P = 0.26

P = 0.15
## Tentative QCA Results

*(F/u: 164±66 days)*

<table>
<thead>
<tr>
<th></th>
<th>Debulking</th>
<th>Non-debulking</th>
<th>n.s.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre</strong></td>
<td><strong>Lesion Length (mm)</strong></td>
<td>13.0±8.5</td>
<td>14.1±9.4</td>
</tr>
<tr>
<td></td>
<td><strong>Reference Diameter (mm)</strong></td>
<td>2.30±0.87</td>
<td>2.33±0.81</td>
</tr>
<tr>
<td></td>
<td><strong>Minimal Lumen Diameter (mm)</strong></td>
<td>0.024±0.15</td>
<td>0.042±0.19</td>
</tr>
<tr>
<td></td>
<td><strong>Diameter Stenosis (%)</strong></td>
<td>99.1±6.1</td>
<td>97.8±11.6</td>
</tr>
<tr>
<td><strong>Post</strong></td>
<td><strong>Reference Diameter (mm)</strong></td>
<td>2.87±0.61</td>
<td>3.01±0.65</td>
</tr>
<tr>
<td></td>
<td><strong>Minimal Lumen Diameter (mm)</strong></td>
<td>2.11±0.55</td>
<td>2.22±0.58</td>
</tr>
<tr>
<td></td>
<td><strong>Diameter Stenosis (%)</strong></td>
<td>25.6±13.8</td>
<td>25.8±13.1</td>
</tr>
<tr>
<td><strong>F/u</strong></td>
<td><strong>Reference Diameter (mm)</strong></td>
<td>2.60±0.63</td>
<td>2.61±0.68</td>
</tr>
<tr>
<td></td>
<td><strong>Minimal Lumen Diameter (mm)</strong></td>
<td>1.64±0.68</td>
<td>1.57±0.77</td>
</tr>
<tr>
<td></td>
<td><strong>Diameter Stenosis (%)</strong></td>
<td>37.0±22.4</td>
<td>41.5±25.5</td>
</tr>
<tr>
<td></td>
<td><strong>Binary Restenosis Rate</strong></td>
<td>21.0%</td>
<td>26.2%</td>
</tr>
</tbody>
</table>

*DOCTORS Investigators*
Lumen Dynamics - QCA

- Acute gain: Debulking 2.10 mm, Non-debulking 2.18 mm
- Late loss: Debulking 0.46 mm, Non-debulking 0.65 mm
- Net gain: Debulking 1.64 mm, Non-debulking 1.53 mm
- Loss index: Debulking 0.20, Non-debulking 0.29

- P-values:
  - Acute gain: P=0.28
  - Late loss: P=0.040
  - Net gain: P=0.29
  - Loss index: P=0.087

(F/u: 164±66 days)
Summary

1. Both RA and DCA could be performed safely in selected CTO cases and facilitated subsequent stent implantation.

2. Pre-stent plaque debulking reduced the need of target vessel revascularization.
Reduction of Restenosis

Japanese Multi-Center Experience
(retrospective analysis)

Restenosis Reocclusion

ALL (n=123)
Non-stent (n=59)
Stent (n=64)

Definition of CTO
- TIMI flow grade = 0
- Occlusive duration ≥ 1Mo
- Restenosis: Fu DS ≥ 50%

(JCS 1999)
Debulking Of Chronic Total Occlusion with RA before Stenting (DOCTORS)

Pilot Study
Study Institutions

- Takeda Hospital
- Kyoto Katsura Hospital
- Osaka Medical Center
- Rinku General Medical Center
- Niigata City General Hospital
- Shiga Medical Center
- Gifu Prefectural Hospital
- National Toyohashi Higashi Hospital

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# Post Procedural Results

1. Procedural success: 99%

2. Patient success: 99%

3. Complication:
   - Death: 0%
   - Em-CABG: 0%
   - AMI: 0%
   - Coronary rupture (RA distal site): 1%

4. Final TIMI flow grade
   - TIMI = 2: 1%
   - TIMI = 3: 99%
### 6M Follow-up Results

(N=100)

1. **Death**
   - **Cardiac**: 2 (1M: infectious pericarditis)
   - **Non-cardiac**: 2 (6M: sudden death)

2. **Q-wave MI**: 0

3. **Unstable angina**: 2

4. **Angiographic Fu**
   - **CABG**: 0
   - **Repeated PTCA**: 24 (29.6%) → TLR rate

---

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Predictors of TLR

Occlusion Length

P=0.21

24.4% (n=45)

37.5% (n=32)

< 20mm

20mm ≤
Predictors of TLR

Total Stent Length

P = 0.0045

- < 20mm: 10.3% (n=29)
- 20mm ≤: 40.4% (n=52)
Predictors of TLR

Max. Burr / Balloon Ratio

- Max. Burr / Balloon Ratio: (n=60) 31.7% (n=21) 23.8%
- P=0.50

(n=60) (n=21)
IVUS Used

Debulking arm

Non-debulking arm

使用 未使用 不明

使用 未使用 不明